determining a level of methylation of a TMS1 nucleic acid molecule in a biological sample from a subject having cancer, and

G4 comparing the level of methylation of the TMS1 nucleic acid molecule in the biological sample to a control,

wherein the TMS1 nucleic acid molecule comprises a CpG island and is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4, and which code for a TMS1 polypeptide comprising a caspase recruiting domain and having apoptosis inducing activity, wherein the stringent conditions are 65°C and 3.5X SSC, and

(b) complements of (a), and

wherein an increase in the level of methylation of the TMS1 nucleic acid molecule in the biological sample compared to the control identifies a subject who is at risk of being non-responsive to an apoptosis-dependent anti-cancer therapy.

Remarks

The specification has been amended to recite "0.015M" rather than "0.15M" sodium citrate in the composition of hybridization buffer component SSC. This was an inadvertent typographical error. Support for this amendment can be found in any standard molecular biology textbook such as Current Protocols in Human Genetics (page A.2D.8, see Appendix B) which teaches the composition of 20x SSC to be 3 M NaCl and 0.3 M sodium citrate. Accordingly, 1x SSC comprises 0.15 M NaCl and 0.015 M sodium citrate. The documentation submitted herewith in Appendix B supports the change in the concentration of citrate in the stringent conditions recited in the specification. This error is considered an obvious error, and thus its correction does not constitute new matter. (See MPEP §2163.07 II "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).")

Claims 1, 47, 123 and 124 have been amended. Claims 1 and 47 have been amended in view of the Examiner's proposed claim amendment. Claims 123 and 124 also have been amended to include the limitations suggested by the Examiner. Support for these amendments can be found on page 3, lines 21-25 and page 16, lines 19-21. Applicant points out that the claims are intended to capture analysis of both a full length TMS1 nucleic acid molecule and a CpG island deriving from a TMS1 nucleic acid molecule, and that the information so derived is indicative of the methylation of a TMS1 nucleic acid molecule as defined in the claims. Methods for detecting methylation are described in the specification at least on page 41, lines 34-36, and pages 42-44.

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Applicant also cancels non-elected claims 5, 13, 15, 18, 21, 22, 30, 38, 58, 61, 67, 68, 71, 72, 89, 95, 101 and 105. Applicant reserves the right to pursue the subject matter of non-elected claims in continuing applications.

Claims 1, 47 and 110-124 are currently pending.

No new matter has been added.

Previously Filed Information Disclosure Statement

Applicant previously submitted an Information Disclosure Statement and modified Form 1449 listing GenBank sequences AF184072, AF184073 and AF255794. The dates on the modified Form 1449 were listed as February 2, 2001. Applicant wishes to clarify that the submission dates of these sequences are September 9, 1999 (AF184072 and AF184073) and April 13, 2000 (AF255794). The February 2, 2001 date represents the latest information update. In this case, Applicant updated the database information to include the publication of a manuscript. This update did not change the sequence information originally submitted.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 47 and 110-124 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Examiner, the specification is enabling for determining the level of methylation using SEQ ID NO:4, the CpG island within the TMS1 nucleic acid, but it does not reasonably provide enablement for correlating any nucleic acid which hybridizes to SEQ ID NO:4 to indicate cancer. The Examiner has proposed an amendment to claims 1 and 47, and Applicant has entered that amendment substantially as proposed. It is to be understood that the claims cover analysis of methylation of a TMS1 nucleic acid molecule, as defined in the claims, regardless of whether the full length TMS1 nucleic acid molecule is used or whether a fragment of the TMS1 nucleic acid molecule is used (e.g., the CpG island alone).

With respect to the latter amendment, Applicant traverses the Examiner's statement that "while claim 1 (as previously pending), required that the nucleic acid encode a native TMS1 polypeptide, the specification does not teach how to identify a molecule that is a TMS1 polypeptide either by assay or specific structure." To the contrary, the specification teaches that "one function of native TMS1 polypeptides is apoptosis induction", and then teaches various ways in which apoptosis induction can be assayed. (See page 17, lines 29-36, and page 18, lines 1-7.) Thus, Applicant believes that the claims as previously pending were indeed enabled; however, in an earnest attempt to expedite prosecution, Applicant has amended the claims substantially as proposed by the Examiner.

In view of these amendments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph, enablement.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 47 and 110-124 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the Examiner, the term "stringent conditions" is a relative term and may have different meanings to artisans in the art. The Examiner has proposed introducing "stringent conditions are 65°C and 3.5X SSC" into claims 1 and 47. Applicant has made these amendments. Support for these amendments can be found on page 19, lines 14-15.

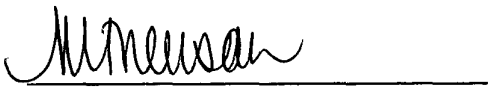
The Examiner also considers claims 1, 47, and 110-122 indefinite because it is unclear whether the CpG island contains the TMS1 nucleic acid or whether the TMS1 nucleic acid contains the CpG island. The specification explicitly states that SEQ ID NO:4, which corresponds to a CpG island, is present in SEQ ID NO:1, which corresponds to a TMS1 nucleic acid molecule. (See Brief Description of the Sequence Listing.) Notwithstanding this, Applicant has amended claims 1 and 47 as well as claims 123 and 124 to clarify that the CpG island is contained within a TMS1 nucleic acid molecule.

In view of these amendments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

Summary

Applicant believes that each of the pending claims is now in condition for allowance. Applicant respectfully requests that the Examiner telephone the undersigned in the event that the claims are not found to be in condition for allowance. If the Examiner has any questions and believes that a telephone conference with Applicant's representative would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Ext. 266).

Respectfully submitted,



Maria A. Trevisan Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210-2211
(617) 720-3500

Docket No.: E00355.70003.US
Date: November 8, 2002
x11.08.02

APPENDIX A:

MARKED-UP SPECIFICATION

Please amend the paragraph beginning on page 19, line 3, as indicated below. For clarity, and in view of the underlined text pre-existing in this paragraph, the amended region is highlighted.

Homologs and alleles of the TMS1 nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for TMS1 polypeptides and which hybridize to a nucleic acid molecule consisting of the coding region of preferably SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:24, or in other embodiments SEQ ID NO:20, SEQ ID NO:22, or in still other embodiments SEQ ID NO:26, and in yet other embodiments SEQ ID NO:5, SEQ ID NO:7 or SEQ ID NO:9, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/[0.15M] 0.015M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2x SSC at room temperature and then at 0.1x SSC/0.1% SDS at temperatures up to 68°C.

MARKED-UP CLAIMS

Please amend the claims as follows:

1. (Twice Amended) A method for identifying a subject at risk of developing a cancer characterized by abnormally increased methylation of a CpG island containing TMS1 nucleic acid molecule comprising

determining a level of methylation of a CpG island [containing] of a TMS1 nucleic acid molecule in a biological sample from a subject, and

comparing the level of methylation of the CpG island [containing] of the TMS1 nucleic acid molecule in the biological sample to a control

wherein the CpG island [containing] of the TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4 [and which code for a native TMS1 polypeptide], wherein the stringent conditions are 65°C and 3.5X SSC, and

(b) complements of (a), [and]

wherein the TMS1 nucleic acid molecule codes for a TMS1 polypeptide comprising a caspase recruiting domain and having apoptosis inducing activity, and

wherein an increase in the level of methylation of the CpG island [containing] of the TMS1 nucleic acid molecule in the biological sample compared to the control identifies a subject at risk of developing the cancer.

47. (Twice Amended) A method for identifying a subject having cancer who is at risk of being non-responsive to an apoptosis-dependent anti-cancer therapy comprising:

determining a level of methylation of a CpG island [containing] of a TMS1 nucleic acid molecule in a biological sample from a subject having cancer, and

comparing the level of methylation of the CpG island [containing] of the TMS1 nucleic acid molecule in the biological sample to a control,

wherein the CpG island [containing] of the TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4 [and which code for a native TMS1 polypeptide], wherein the stringent conditions are 65°C and 3.5X SSC, and

(b) complements of (a), [and]

wherein the TMS1 nucleic acid molecule codes for a TMS1 polypeptide comprising a caspase recruiting domain and having apoptosis inducing activity, and

wherein an increase in the level of methylation of the CpG island [containing] of the TMS1 nucleic acid molecule in the biological sample compared to the control identifies a subject who is at risk of being non-responsive to an apoptosis-dependent anti-cancer therapy.

123. (New) A method for identifying a subject at risk of developing a cancer characterized by abnormally increased methylation of a TMS1 nucleic acid molecule [comprising a TMS1 CpG island] comprising

determining a level of methylation of a TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in a biological sample from a subject, and

comparing the level of methylation of the TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in the biological sample to a control

wherein the TMS1 nucleic acid molecule comprises a CpG island and [comprising a TMS1 CpG island] is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4, and which code for a TMS1 polypeptide comprising a caspase recruiting domain and having apoptosis inducing activity, wherein the stringent conditions are 65°C and 3.5X SSC, and

(b) complements of (a), and

wherein an increase in the level of methylation of the TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in the biological sample compared to the control identifies a subject at risk of developing the cancer.

124. (New) A method for identifying a subject having cancer who is at risk of being non-responsive to an apoptosis-dependent anti-cancer therapy comprising:

determining a level of methylation of a TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in a biological sample from a subject having cancer, and

comparing the level of methylation of the TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in the biological sample to a control,

wherein the TMS1 nucleic acid molecule comprises a CpG island and [comprising a TMS1 CpG island] is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4, and which code for a TMS1 polypeptide comprising a caspase recruiting domain and having apoptosis inducing activity, wherein the stringent conditions are 65°C and 3.5X SSC, and

(b) complements of (a), and

wherein an increase in the level of methylation of the TMS1 nucleic acid molecule [comprising a TMS1 CpG island] in the biological sample compared to the control identifies a subject who is at risk of being non-responsive to an apoptosis-dependent anti-cancer therapy.